UNCOUPLING CD39 AND T CELL ANTIGEN SPECIFICITY IN BRAIN TUMORS
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Background Tumor-infiltrating lymphocytes have long been thought to encompass a repertoire recognizing primarily tumor antigens. However, our lab and others have found that tumor-infiltrating CD8+ T cells include a population with viral specificity which can often outnumber tumor-reactive cells. Thus, identifying markers of tumor-reactive T cells are critical for developing ways to target this sub-population and boost anti-tumor immunity. Work to this end has defined CD39 and CD103 as putative markers of tumor-reactive T cells in several solid tumors. CD39+ CD8+ T cells have impaired cytokine production and increased expression of inhibitory receptors, while CD39- CD8+ T cells lack hallmarks of chronic antigen stimulation, highlighting their bystander role.

Methods In contrast, we unexpectedly found that CD39 is highly expressed on functional virus-specific CD8+ T cells in healthy brain compared to other non-lymphoid tissues examined. These findings prompted us to investigate whether the established CD39 antigen-specificity paradigm held true in brain tumors. To test this, we established a mouse model of glioblastoma (GBM) and melanoma brain metastasis harboring virus-specific memory T cells, similar to the observations found in humans.

Results Surprisingly, we found that CD39 expression was uniformly high on all CD8+ T cells in both brain tumor models, including on virus-specific T cells which also co-expressed CD103. Moreover, these CD39+ antiviral T cells remained functionally active and could mediate local inflammation upon recognition of cognate antigen. In contrast, in a mouse model of primary melanoma, bystander virus-specific T cells did not express CD39 while the bulk CD8+ population, including tumor-reactive T cells, expressed high CD39 as has been demonstrated clinically.

Conclusions Our ongoing studies aim to elucidate the functional role of CD39 in T-cell mediated immunity of brain tumors. Overall, these data suggest that CD39 may not stratify tumor-reactive CD8+ T cells in brain tumors as has been demonstrated in other solid tumors. Thus, therapeutic approaches to target CD39/CD103+ T cells or restore anti-tumor immunity through CD39 blockade may have different clinical implications in tumors of the central nervous system.